REMARKS

Status of the Claims.

Claims 1, 4-9, and 23-28 are pending with entry of this amendment. Claims 1, 4, 6, 7, and 23-27 are amended herein.

Support for the amendment to Claim 1 is found in the specification at least at page 5, lines 30-32, taken with page 45, lines 43-47. Additional support for this amendment is evident upon comparing page 6, lines 1-14, with page 6, line 18 to page 7, line 2. The remaining amendments are intended to conform the language in Claims 4, 6, 7, and 23-27 to this and previous amendments to Claim 1. Thus, none of the amendments introduce new matter.

In addition, none of the amendments is believed to change the scope of the formerly pending claims.

Petition for Withdrawal of Finality of Office Action.

This Amendment is accompanied by a Petition for Withdrawal of Finality of Office Action. As stated in the Petition, Applicants submit that final rejection of the claims was premature in light of Applicants' extensive amendments to the claims in the Preliminary Amendment filed in the present application on August 7, 2000. Accordingly, withdrawal of the finality of the outstanding Office Action is respectfully requested.

Examiner Interview.

Applicants' Attorney appreciates the courtesy extended by Examiner Hines and Smith in an interview on January 4, 2001. All of the outstanding rejections were discussed and the points raised during the interview are reiterated below.

35 U.S.C. §112, First Paragraph.

Claims 1, 4-9, and 23-27 were rejected under 35 U.S.C. §112, first paragraph because the Examiner believed that the reference in Claim 1 to "individual microspheres" having an *in vitro* antigen release profile characterized by three phases was not supported in the specification. The rejection is respectfully traversed.

During the interview, Examiner Hines stated that she did not believe that the passage cited in the Preliminary Amendment (filed August 7, 2000) supported the language "individual microspheres." Applicant's Attorney explained that the language was included in

Claim 1 to clarify that Claim 1 was drawn to a particular embodiment of the invention described in the application. The invention relates to "microspheres that release . . . antigen and/or adjuvant in three phases: an initial burst, a slow release, and a second burst."[1] An important aspect of the invention is the relative timing of the initial and second burst, as these provide an initial immunization with antigen (i.e., the initial burst), followed, after an appropriate interval, by a booster immunization (i.e., the second burst). *See* Applicants' specification, at 5, lines 30-32. Page 45, lines 43-47, of the specification states that "the microspheres are preferably designed to produce an in vitro second burst at the same time." Thus, the timing between the initial and second burst is the same for the microspheres in a particular population.

Such a population is described in the application at page 6, lines 1-14, which relates to a composition comprising microspheres sharing the described properties. This microsphere population represents one embodiment of the invention originally described in the application. A second embodiment is described in a later passage on page 6, which relates to a composition containing multiple populations of microspheres with different properties. *See* Applicants' specification, at 6, line 18-page 7, line 2. Specifically, this later passage states:

> Another aspect of the invention is a composition for use as a vaccine comprising about one to 100 antigens encapsulated in ***a mixture of about two to 50 PLGA microsphere populations***, wherein
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> * * *
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> the antigen is released from the microspheres in a triphasic pattern, wherein about 0.5 to 95% of the antigen is released in an initial burst, about 0 to 50% is released over a period of about 1 to 180 days, and the remaining antigen is released in a second burst in ***one microsphere population*** after about 1 to 30 days, in ***a second microsphere population*** after about 30 to 90 days, and in ***additional microsphere populations*** after about 90 to 180 days.

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[1] The "initial burst" corresponds to the "first antigen burst phase" recited in Claim 1; the "slow release" corresponds to the "second slow release phase" of Claim 1; and the "second burst" corresponds to the "third antigen burst phase" of Claim 1. Thus, as used in Claim 1, the terms "first," "second," and "third" refer to the first, second and third phases of the triphasic release profile, and the release of antigen during each phase is referred to in Claim 1 as "antigen bursts" in the first and third phases, separated by a "slow release" in the second phase.

(Emphasis added.) This passage clearly refers to a mixture of microsphere populations wherein each population has a release profile that differs from that of the other populations. Thus, this second embodiment of the invention relates to mixed populations, wherein each population has a characteristic release profile.

Considering the first embodiment described above in conjunction the second embodiment, one of skill would readily appreciate that the first embodiment relates to a composition comprising an "un-mixed" population of microspheres that is homogeneous with respect to release profile. An important aspect of this embodiment is ***a specific triphasic release profile***, which is designed to release antigen in a manner that is advantageous for vaccine delivery, ***is achieved using a single homogeneous population of microspheres***.

The second embodiment is actually a variation of the first embodiment. That is, the second embodiment relates to a composition comprising a mixture of populations, wherein each population is homogeneous with respect to release profile. Each homogeneous population exhibits a specific triphasic release profile, as in the first embodiment. However, the timing of the second burst can be different in each population. In particular, the second burst is described as occurring "after about 1 to 30 days" for one population, "after about 30 to 90 days" for a second population, and "after about 90 to 180 days" for additional populations. One of skill in the art understands that this description relates to a composition in which multiple homogeneous microsphere populations, of the sort described in the first embodiment, can be combined to give a composition that has a release profile with more than three phases.

Applicants had previously amended Claim 1 to recite "individual microspheres" having the triphasic release profile recited in Claim 1 to clarify that Claim 1 is drawn to the first embodiment. In other words, Claim 1 relates to a composition including a homogeneous population of microspheres that exhibits a specific triphasic release profile. Applicants wish to emphasize that Claim 1 is an open-ended "comprising" claim and, therefore, reads on any composition including at least one such population of microspheres, regardless of the presence of other microsphere populations or other components. Thus, Claim 1 encompasses the second embodiment described above.

The language "individual microsphere" was intended to capture the notion of a population of microspheres wherein the individual microspheres in the population share a common triphasic release profile. In other words, the language was intended to clarify that Claim 1 recited a population of microspheres that was homogeneous. During the interview,

however, Examiner Smith indicated that the term "homogeneous population" was more clearly supported by the specification cited above than the term "individual microspheres." Accordingly, in an effort to expedite prosecution, Applicants have amended Claim 1 to delete the reference to individual microspheres and to insert appropriate references to a homogenous population of microspheres.

Applicants emphasize that this amendment is not believed to change the scope of the claims, but merely represents an alternative expression of the same concept. As the Examiners agreed that this alternative expression finds support in the application, Applicants respectfully request withdrawal of the §112, first paragraph rejection. If the Examiner believes that this rejection cannot be withdrawn, an interview is requested.

35 U.S.C. §103(a).

The Rejections

The pending claims are rejected under 35 U.S.C. §103(a) over various combinations of references. Specifically, Claims 1, 4-9, and 23-28 are rejected as unpatentable over Sanders et al., in view of Eldridge et al., and further in view of Jeffery et al. Claims 5-7 are rejected as unpatentable over the Sanders-Eldridge-Jeffery combination taken with Wang et al. Claim 8 is rejected as unpatentable over the Sanders-Eldridge-Jeffery combination taken with Newman et al. Claims 1, 4, 9, and 23-28 are rejected as unpatentable over Floy et al., and Claims 5-7 are rejected as unpatentable over Floy et al., Sanders et al. in view of Immunization Practices Advisory Committee recommendations. Each of these rejections is respecfully traversed.

The citations and a detailed description of the teachings of these references can be found in the Preliminary Amendment (filed August 7, 2000).

The Invention

During the interview, Applicants' Attorney discussed at length particular features of the invention that set the invention apart from all of the art of record, and Examiners Hines and Smith requested that this discussion be included in Applicants' response to the Office Action.

As stated in the interview, Applicants do not purport to have discovered that polylactide or poly(lactide-co-glycolide) polymers (collectively referred to as "PLGA polymers") exhibit triphasic release. Accordingly, Applicants have not claimed a composition comprising PLGA polymers that exhibit ***any*** triphasic release profile. Instead, the claims

recite a composition comprising "a homogeneous population of polylactide or poly (lactide-co-glycolide) (PLGA) polymer microspheres" having a ***specific*** triphasic release profile. This specific triphasic release profile is designed to release antigen in a manner that is advantageous for vaccine delivery. Thus, Claim 1 also recites that the microspheres encapsulate an antigen.

In developing this invention, Applicants had to: (1) decide upon a desirable antigen release profile, (2) select a homogeneous population of PLGA microspheres as a delivery material capable of releasing antigen with this profile, and (3) determine how to make a composition including a homogeneous population of PLGA and encapsulated antigen that would, in fact, provide the desired release profile. As the record amply demonstrates, this work was carried out during a time when researchers studying the use of PLGA microspheres for drug delivery were largely focused on preparing composition that provided essentially continuous release of drug. *See* discussions of Sanders in this and previous Office Action responses. For these researches, the triphasic release characteristics of PLGA microspheres was a disadvantage to be minimized. This work was aimed at "flattening out" the peaks and valley in the triphasic release profile, i.e., reducing the size of the initial burst and increasing release in the subsequent slow release phase.

By contrast, the present invention exploits the triphasic release characteristics of PLGA polymers to provide a specific, desirable release profile suitable for use in delivering a vaccine. That is, the inventors discovered how to time the peaks and valley of the release profile to arrive at a release profile that was particularly well-suited to vaccine delivery. Thus, the inventors determined how to make microspheres that would release an initial burst of antigen that was sufficient to provide an initial immunization. This initial burst was followed, after an appropriate time lag, by a second burst of antigen that was sufficient to act as a booster immunization. The development of this invention required the inventors to ***control, rather than reduce or eliminate, the triphasic release of PLGA polymers***. This approach was diametrically opposed to that of the research relating to the use of PLGA polymers for delivery of conventional drugs.

As Examiner Hines has noted, however, other researchers have investigated the use of PLGA polymers to deliver vaccines. *See* discussions of Eldridge and Jeffery in this and previous Office Action responses. But as the extensive prosecution history of this application makes clear, there is no evidence that other researchers even attempted to make a composition having the specifically recited release profile or one that achieved this profile

using a single homogeneous population of microspheres. One group (Eldridge et al.), in particular, recognized that multiphasic release could be employed for vaccine delivery and even experimented with PLGA polymers for this purpose. However, in this work, the timing of initial and second bursts was manipulated by mixing different populations of microspheres, i.e., one that provided an initial burst and one that provide a second burst. This work represents a completely different approach to the problem of how to control the timing of multiple release phases. Whereas others mixed populations to achieve triphasic release, Applicants produced a homogeneous population of microspheres that exhibited a desirable triphasic release profile.

Moreover, the release profile recited in Claim 1 is distinct from any release profile described in the references of record. Although a wide variety of different vaccine regimens can be found in the art, Applicants selected one, from among myriad possibilities, that could be achieved using a homogeneous PLGA population.

Finally, Applicants have also taught how to make such a population. The prosecution history of the present case suggests that the Patent Office regards this work as "routine optimization." However, as evidenced by the grant of U.S. Patent No. 6,080,429 (issued June 27, 2000 to Cleland et al.), the discovery of a method for making a homogeneous microsphere population such as that claimed represented a patentable advance, despite the record demonstrating that much was known about the production of PLGA microspheres.

In summary, Applicants' contribution to the art included, at least, (1) determining a ***specific*** desirable antigen release profile, (2) selecting a ***homogeneous*** population of PLGA microspheres as a delivery material capable of releasing antigen with this release profile, (3) demonstrating ***how to make*** such a microsphere population. This work represents an important advance, as vaccines based on homogeneous microsphere populations can be easily manufactured (i.e., without the need for mixing populations) and can be delivered in a single shot. Such "single-shot" vaccines are seen as perhaps the only viable means of vaccinating populations in areas where access to medical care is limited.

The Legal Requirements for a Prima Facie Case of Obviousness

As stated during the interview, Applicants submit that no *prima facie* case of obviousness has been established in the present application. The three elements of a prima facie case of obviousness are (1) the reference(s) must teach or suggest all of the elements of the claimed invention, (2) there must some motivation for combining or modifying the teachings of the references to arrive at the claimed invention, and (3) the reference(s) or

knowledge in the art must provide a reasonable expectation of success, i.e., a reasonable assurance that the claimed invention would work. As discussed in greater detail below, Applicants submit that none of these elements have been satisfied in the present application.

Much of the attention during prosecution has focused on what was known generally about PLGA polymers prior to the filing date of the invention. The specifics of the invention have been dismissed as mere optimization. This treatment is directly contrary to Federal Circuit precedent. *In Re Kotzab*, 217 F.3d 1365; 2000 U.S. App. LEXIS 15504; 55 USPQ2d 1313 (Fed. Cir. 2000) emphasizes the need for specificity in the obviousness inquiry as follows:

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2D (BNA) at 1617. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." *Id.* (quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. (BNA) 303, 313 (Fed. Cir. 1983)).
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> Most if not all inventions arise from a combination of old elements. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2D (BNA) 1453, 1457 (Fed. Cir. 1998). Thus, every element of a claimed invention may often be found in the prior art. *See id.* However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. *See id.* Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, ***there must be some motivation, suggestion or teaching of the desirability of making the specific combination*** that was made by the applicant. *See In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2D (BNA) 1635, 1637 (Fed. Cir. 1998); *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. (BNA) 1125, 1127 (Fed. Cir. 1984). Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. *See B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582, 37 U.S.P.Q.2D (BNA) 1314, 1318 (Fed. Cir. 1996).
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> The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved. *See Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2D (BNA) at 1617. In

> addition, the teaching, motivation or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. *See WMS Gaming, Inc. v. International Game Tech.*, 184 F.3d 1339, 1355, 51 U.S.P.Q.2D (BNA) 1385, 1397 (Fed. Cir. 1999). The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. *See In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. (BNA) 871, 881 (CCPA 1981) (and cases cited therein). ***Whether the Board relies on an express or an implicit showing, it must provide particular findings related thereto.*** *See Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2D (BNA) at 1617. ***Broad conclusory statements standing alone are not "evidence."*** Id.
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> [A] rejection cannot be predicated on the mere identification in Evans of individual components of claimed limitations. Rather, ***particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.***

In re Kotzab, at 1369-1372 (emphasis added).

The Cited Combinations of References

Applicants respectfully submit that none of the cited combinations of references satisfy the requirements for a prima facie case of obviousness, and further that all of the cited combinations are particularly deficient with respect to providing specific motivation for the claimed invention.

The Sanders-Eldridge-Jeffery Combinations

Claim 1 recites a "composition comprising a ***homogeneous*** population of polylactide or poly (lactide-co-glycolide) (PLGA) polymer microspheres encapsulating an ***antigen***, wherein . . .

> ***the microspheres in said homogeneous population have an in vitro antigen release profile characterized by three phases***: a first antigen burst phase, wherein about 0.5 to 30 percent of the antigen is released from the microspheres over a period of about three days after suspension of the microspheres in a release medium; a second slow release phase after the first phase, extending from about the fourth to at least about the thirtieth day after suspension, wherein the daily release of antigen from the microspheres is less than in the first antigen burst phase or a third antigen burst phase; and the third antigen burst phase after the second phase, wherein antigen is released from the microspheres at a rate of greater than 10 percent

per week, during a period of from about seven to about 30 days, starting from about 30 to about 180 days after suspension.

The bolded text above is intended to highlight the combination of elements that is neither taught nor suggested by the references of record, i.e., a (1)homogeneous population of microspheres, that (2) encapsulates an antigen and (3) has the recited release profile. As Claim 1 is the only pending independent claim, the distinctions over the art of record are discussed below with respect to this claim.

The Sanders-Eldridge-Jeffery combination clearly fails to teach the recited release profile. To reiterate from the Preliminary Amendment:

> [N]one of the references teach or suggest microspheres having a first antigen burst phase wherein about 0.5 to 30 percent of the antigen is released from the microspheres during the first three days. Nor do any of the references teach or suggest microspheres having a second slow release phase extending from about the fourth to at least about the thirtieth day after suspension wherein the daily release of antigen is less than that of the first or third antigen burst phases.

Preliminary Amendment dated August 7, 2000, at 9 (emphasis omitted).

The Examiner appears to concede this point, but urges that:

> Sanders et al, specifically teaches microspheres that have triphasic release profiles and models which provide for the reliable indication of the duration of compound release. Sander et al., [*sic*] also teaches several factors such as parameters of the copolymer, the molecular weight and polymer composition, and intrinsic viscosity that affect the release profile. Further, Eldridge et al. Teaches [*sic*] using a combination of variables to achieve discrete releases of antigens.

Office Action, at 4. Without endorsing this characterization of the references, Applicants submit that these statements are insufficient to establish a *prima facie* case of obviousness.

Applicants earnestly request the Examiner to consider ***why*** one skilled in the art would combine these references and modify their teachings to arrive at the specifically claimed invention. The Office Action states that "the combined teachings of the prior art suggest to a person of skill in the art that compositions containing various volumes of antigen can be encapsulated into microspheres for controlled release of antigen." Perhaps . . . ., but the combined teachings of the prior art fail to suggest the ***recited*** antigen release profile. Well-established Federal Circuit precedent makes it clear that obviousness cannot be

established merely by showing that the invention would have been possible, in the absence of some specific reason for developing the invention. *See* M.P.E.P. § 2143.01 (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Thus, even assuming *arguendo* that a person of skill in the art could have made microspheres having the recited profile, no *prima facie* case is established if the art fails to suggest a reason for doing so. The record is devoid of any such reason.

As detailed in the previously filed Preliminary Amendment, Sanders represents the art concerning the use of PLGA to deliver a conventional drug. One of skill in the art would understand that, in this context, multiphasic release is undesirable. Thus, any modification of the release profiles in Sanders would be aimed at producing microspheres that approximate continuous release, not microspheres that are deliberately designed to have a particular triphasic release profile.

Eldridge is cited as remedying this deficiency of Sanders. That is, Eldridge is said to teach "combinations of variables to achieve discrete releases of antigens." *Id.* Eldridge represents the art concerning the use of PLGA to administer antigen. This reference suggests that multiphasic release can be used to advantage to deliver antigen, but fails to teach or suggest the ***recited*** antigen release profile. Thus, the general teachings of the Sanders-Eldridge combination fail to teach or suggest one of the key elements of the invention.

Moreover, the specific teachings of Eldridge regarding the utility of multiphasic release and those of Sanders suggesting that such release should be minimized are clearly at odds. An examination of the specific teachings of these references, that takes context into account, makes it clear the only motivation for combining these references is found in Applicants' specification.

Finally, in the invention of Claim 1, a desired triphasic release profile is obtained using a homogeneous population of microspheres. By contrast, Eldridge achieves control over the release profile by mixing populations of microspheres. This represents a fundamentally different solution to the problem of how to manipulate the release profile of PLGA polymers than that recited in the pending claims. Whereas, the claimed invention enables one to produce a ***homogeneous*** population of microspheres having the recited triphasic release profile in one polymerization reaction, Eldridge teaches that at least two microsphere populations are prepared and mixed. Nothing in Sanders speaks to this point.

Thus, nothing in the Sanders-Eldridge combination teaches or suggests this additional important element of the invention.

The Office Action is silent with respect to the teachings of Jeffery, the third reference in the cited combination. Jeffery was cited by the previous Examiner for the "incorporation of antigens in poly(lactide-co-glycolide) systems," with the previous Examiner conceding that Jeffery does not teach triphasic release. Office Action dated March 17, 1999, at 5. Jeffery additionally taught the use of smaller microspheres than recited in Applicants' claims. Applicants have demonstrated that alteration of production parameters of PLGA microspheres leads to dramatically different release characteristics, and Eldridge and Jeffery both showed that particles as small as those used by Jeffery are rapidly phagocytized and degraded so that triphasic release would not be possible from such microspheres. Thus, the Sanders-Eldridge-Jeffery combination fails to teach a homogeneous population of microspheres that encapsulate antigen and have the recited release profile and furthermore, fails to provide any specific motivation for making such a population.

Moreover, the record is devoid of any reasonable expectation that such a population of microspheres could be produced. The rationale for the rejection appears to assume that art was developed to a point that one of skill could produce a homogeneous population of PLGA microspheres having any desired profile. To support this position, the Examiner has cited evidence that a number of the parameters that affect the release characteristics of PLGA polymers were known before the filing date of the invention. But such evidence does not indicate that any desired release profile could be achieved. Nor does this evidence establish that the interactions among the various parameters affecting release were sufficiently well-understood that one skilled in the art would know that a particular combination of parameters would produce a homogeneous population of microspheres with the recited release profile. Accordingly, the prior art does not provide any reasonable assurance that the claimed population of microspheres could be produced.

The Wang reference was added to the Sanders-Eldridge-Jeffery combination for the purpose of rejecting Claims 5-7. As stated in the Preliminary Amendment:

> Claims 5-7 depend, directly or indirectly, from Claim 1 and recite a composition "further comprising an adjuvant." Wang was cited by the Examiner for the proposition that it was known in the art of vaccination to combine adjuvants with antigens for release from microspheres. Office Action 3/17/99, page 6, first paragraph. ***The microspheres of Claim 1 have been distinguished above. Wang***

> ***does not provide a teaching or suggestion of a triphasic release profile meeting Applicants' claim limitations that would remedy that deficiency in the primary references.*** The Examiner noted as much in the Office Action, stating that "Wang is not directed to triphasic release pattern" (page 6, first paragraph).

Preliminary Amendment dated August 7, 2000 (emphasis added), at 10. In response to these remarks, the Examiner stated that "one cannot show nonobviousness by attacking the references individually where the rejections are based on combinations of rejections." Office Action, at 4-5. Applicants direct the Examiner's attention to the bolded text in the above quotation which should make it clear that Applicants were not "attacking the references individually." Rather, Applicants referred to the previous discussion for the distinctions over Sanders, Eldridge, and Jeffery and then stated that Wang failed to supply the elements of the invention that were missing from the three previously discussed references. Applicants submit that the same is true of the present Amendment; i.e., like Sanders, Eldridge, and Jeffery, Wang fails to teach or suggest a homogeneous population of microspheres that encapsulate antigen and have the recited release profile, fails to provide any motivation for making such a population, and fails to provide any reasonable assurance that such a population could be made. If the Examiner maintains this rejection, the Examiner is respectfully requested to address these points.

The Newman reference was added to the Sanders-Eldridge-Jeffery combination for the purpose of rejecting Claim 8. As stated in the Preliminary Amendment, Newman is cited simply for its teaching of QS21 and fails to remedy the deficiencies of Sanders, Eldridge, and Jeffery. Thus, the combination of Sanders, Eldridge, Jeffery and Newman also fails to fails to teach or suggest a homogeneous population of microspheres encapsulating antigen and having the recited release profile, fails to provide any motivation for making such a population, and fails to provide any reasonable assurance that such a population could be made.

In conclusion, the combinations of references based on Sanders, Eldridge, and Jeffery fail to satisfy any of the requirements for a *prima facie* case of obviousness. Applicants therefore respectfully request withdrawal of the 103 rejection over the combinations of references including Sanders, Eldridge, and Jeffery.

Floy

In support of the 103 rejection over Floy, the Examiner stated:

> Applicant argues [*sic*] that Floy et al., presents no new data and does not teach or suggest the element of triphasic releases [*sic*]. Applicants mere arguments do not equate to evidence to the contrary or evidence of unexpected results.

Office Action, at 6. Applicants respectfully point out that, under the law, Applicants have no obligation to present such evidence until the Examiner has established a *prima facie* case of obviousness. As Applicants stated in the Preliminary Amendment, the general teachings of Floy are insufficient to establish a *prima facie* case. Preliminary Amendment dated August 7, 2000, at 12. Thus, the burden is on the Examiner to make "particular findings . . . as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected . . . [the] components [of the invention] for combination in the manner claimed." *Kotzab (supra)*. More specifically, the burden is on the Examiner to explain how one of skilled would have arrived at a (1) homogeneous population of microspheres, that (2) encapsulates an antigen and (3) has the recited release profile.

In the Office Action, the Examiner stated:

> Floy et al., teaches drug release profiles from microspheres which typically exhibit a triphasic release pattern. Floy et al., also teaches multiple factors which affect the release profiles and that parameters can be varied for optimization of the delivery system. As previously stated, [*sic--if*] the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Office Action, at 6. Applicants believe that the above discussion of the invention makes it clear that Applicants have not merely discovered optimum or workable ranges by routine experimentation. The present invention represents a unique solution to problem of vaccine delivery, which required Applicants to deviate from the paths taken by all others working with PLGA polymers. Those researchers who were working on delivery of conventional drugs, such as Sanders et al., were interested in achieving continuous release. Optimization of this work would have led directly away from the claimed invention. Eldridge et al., who were working on antigen delivery, recognized that multiphasic release could be useful, but achieved control over the timing of antigen bursts by mixing populations of microspheres that had different release characteristics.

The record is devoid of the concept of a homogeneous population of microspheres having a defined triphasic release profile that is specifically tailored to releasing antigen. The invention of such a population cannot properly be characterized as "optimization." Accordingly, Applicants respectfully submit that the above-quoted statements about Floy's general teachings regarding triphasic release and the affect of various parameters on release characteristics do not establish a *prima facie* case of obviousness.

Because Floy fails to teach the claimed microsphere population, fails to provide any specific motivation for making such a population, and fails to provide any reasonable expectation that such a population of microspheres could be produced, the 103 rejection over Floy is improper. Withdrawal of this rejection is therefore respectfully requested.

The Floy-Sanders-Immunization Practices Advisory Committee Report Combinations

In explaining the 103 rejection over the combinations based on Floy, Sanders, and the Immunization Practices Advisory Committee Report (the "IPAC Report"), the Examiner stated only that "it would have been obvious to combine the two elements in a microsphere, absent evidence to the contrary or unexpected results." Office Action, at 6-7. The Office Action is silent as to the elements to which the Examiner refers.

The Examiner's is respectfully requested to consider this rejection in light of the Federal Circuit's pronouncement in *In re Kotzab* (quoted above) that "[b]road conclusory statements standing alone are not 'evidence'" of obviousness. It is difficult to imagine a broader, more conclusory statement that "it would have been obvious to combine the two elements in a microsphere." Accordingly, this statement is unquestionably insufficient to establish a *prima facie* case of obviousness. As stated above, in the absence of a *prima facie* case, the burden of proving non-obviousness does not shift to Applicants.

Moreover, as discussed above, the Sanders and Floy suffer from the same deficiencies, namely, that neither reference teaches or suggests a (1) homogeneous population of microspheres, that (2) encapsulates an antigen and (3) has the recited release profile. Thus, whether taken alone or in combination, Sanders and Floy fail to teach or suggest the claimed invention. Like Sanders and Floy, the IPAC Report fails to teach the combination of these three elements of the invention, fails to provide any specific motivation for combining these elements, and fails to provide any reasonable expectation of success. Thus, the addition of the IPAC Report to Floy and Sanders, therefore does not establish a *prima facie* case.

The Newman reference was added to the Floy-Sanders-Eldridge-IPAC Report combination for the purpose of rejecting Claim 8. Newman is cited simply for its teaching of QS21 and fails to remedy the deficiencies of Floy, Sanders, the IPAC Report. Thus, the combination of Floy, Sanders, the IPAC Report, and Newman also fails to fails to teach or suggest a homogeneous population of microspheres encapsulating antigen and having the recited release profile, fails to provide any motivation for making such a population, and fails to provide any reasonable assurance that such a population could be made.

In conclusion, the combinations of references based on Floy, Sanders, the IPAC Report fail to satisfy any of the requirements for a *prima facie* case of obviousness. Applicants therefore respectfully request withdrawal of the 103 rejection.

Conclusion

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner determines not to issue a Notice of Allowance, an interview is respectfully requested. In addition, if a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (408) 487-1296.

Respectfully submitted,

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APPENDIX A

"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF USSN 08/846,933 WITH ENTRY OF THIS AMENDMENT

1. (Five Times Amended) A composition comprising a homogeneous population of polylactide or poly (lactide-co-glycolide) (PLGA) polymer microspheres encapsulating an antigen, wherein said homogeneous population is produced from an emulsion comprising aqueous antigen and a polylactide or PLGA polymer, and

(a) the polymer has a ratio of lactide to glycolide of about 100:0 to 50:50 weight percent;

(b) the polymer has an inherent viscosity of about 0.1 to 1.2 dL/g;

(c) the microspheres in said homogeneous population have a median diameter of about 20 to 100 μm; and

(d) [individual] the microspheres in said homogeneous population have an *in vitro* antigen release profile characterized by three phases: a first antigen burst phase, wherein about 0.5 to 30 percent of the antigen is released from the microspheres over a period of about three days after suspension of the microspheres in a release medium; a second slow release phase after the first phase, extending from about the fourth to at least about the thirtieth day after suspension, wherein the daily release of antigen from the microspheres is less than in the first antigen burst phase or a third antigen burst phase; and the third antigen burst phase after the second phase, wherein antigen is released from the microspheres at a rate of greater than 10 percent per week, during a period of from about seven to about 30 days, starting from about 30 to about 180 days after suspension.

4. (Amended) The composition of Claim 1 wherein the median diameter of the microspheres in said homogeneous population is about 30 μm.

5. The composition of Claim 1 further comprising an adjuvant.

6. (Amended) The composition of Claim 5 wherein the adjuvant is encapsulated in microspheres.

7. (Amended) The composition of Claim 5 wherein the adjuvant is coencapsulated with the antigen in the microspheres of said homogenerous population.

8. The composition of Claim 5 wherein the adjuvant is QS21.

9. The composition of Claim 1 further comprising a soluble antigen.

23. (Twice amended) The composition according to Claim 1 wherein [antigen release occurs in] the second slow release phase extends over a period of about 30 days.

24. (Twice amended) The composition according to Claim 1 wherein [antigen release occurs in] the second slow release phase extends over a period of about 60 days.

25. (Twice amended) The composition according to Claim 1 wherein [antigen release occurs in] the second slow release phase extends over a period of about 90 days.

26. (Twice amended) The composition according to Claim 1 wherein [antigen release occurs in] the second slow release phase extends over a period of about 120 days.

27. (Twice amended) The composition according to Claim 1 wherein [antigen release occurs in] the second slow release phase extends over a period of about 180 days.

28. The composition of Claim 1 wherein the polymer microspheres are polynucleotide(D-L-lactide-co-glycolide) microspheres.